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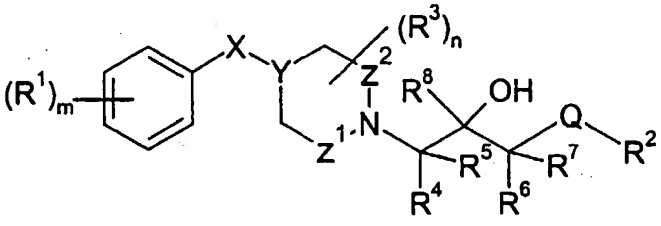
(54) Title: NOVEL COMPOUNDS



(I)

(57) Abstract: The invention provides compounds of general formula (I) wherein m, n, Z^1, Z^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in the specification, process for their preparation, pharmaceutical compositions containing them and their use in therapy.

NOVEL COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

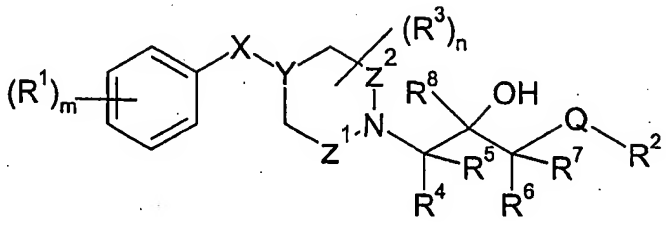
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of general formula



(I)

wherein:

m is 0, 1, 2 or 3;

each R^1 independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^9R^{10}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido ($-SO_2NH_2$), C_1-C_6 alkylsulphonyl, $-C(O)NR^{11}R^{12}$, $-NR^{13}C(O)-(NH)_pR^{14}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

p is 0 or 1;

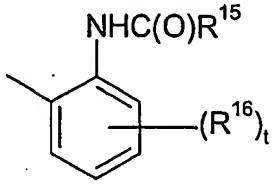
X represents an oxygen atom or a CH_2, OCH_2, CH_2O, CH_2NH, NH, carbonyl or sulphonyl group and Y represents a nitrogen atom or a CH or C(OH) group, provided that when X represents an oxygen atom or a CH_2O, CH_2NH or NH group, then Y represents a CH group;

Z^1 represents a bond or a group $(CH_2)_q$ where q is 1 or 2;

Z^2 represents a bond or a group CH_2, with the proviso that Z^1 and Z^2 do not both simultaneously represent a bond;

Q represents an oxygen or sulphur atom or a group CH_2 or NH;

R^2 represents a group



;

n is 0, 1 or 2;

each R^3 independently represents a C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, -CH_2OH or carboxyl group;

R^4, R^5, R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^4, R^5, R^6 and R^7 together represent a C_1-C_4 alkylene chain linking the two carbon atoms to which they are attached to form a 4- to 7-membered saturated carbocycle, or R^5, R^6 and R^7 each represent a hydrogen atom and R^4 and R^8 together with the carbon atoms to which they are attached form a 5- to 6-membered saturated carbocycle;

R^8 represents a hydrogen atom, a C_1-C_6 alkyl group or is linked to R^4 as defined above;

R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

R^{13} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{14} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl;

R^{15} represents a group C_2-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, adamantyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, wherein each group may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{17}, with the proviso that R^{15} does not represent an unsubstituted 1-pyrrolidinyl, an unsubstituted 1-piperidinyl or an unsubstituted 1-hexamethyleneiminyl (1-homopiperidinyl) group;

t is 0, 1, 2 or 3;

each R^{16} independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl,

C_1-C_6 haloalkoxy, $-NR^{18}R^{19}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido ($-SO_2NH_2$), C_1-C_6 alkylsulphonyl, $-C(O)NR^{20}R^{21}$, $-NR^{22}C(O)(NH)_vR^{23}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

R^{17} represents a C_1-C_6 alkyl, amino ($-NH_2$) or phenyl group;

R^{18} and R^{19} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{20} and R^{21} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

v is 0 or 1;

R^{22} represents a hydrogen atom or a C_1-C_6 alkyl group; and

R^{23} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, an alkyl or alkenyl substituent group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. In the definition of R^{15}, it should be noted that the unsaturated 5- to 10-membered heterocyclic ring system may be aliphatic or aromatic.

The integer m is preferably 1 or 2.

Each R^1 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy); C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), C_1-C_6, preferably C_1-C_4, haloalkoxy (e.g. trifluoromethoxy), $-NR^9R^{10}$, C_3-C_6 cycloalkylamino (e.g. cyclopropylamino, cyclobutylamino, cyclopentylamino or

cyclohexylamino), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), sulphonamido, C_1-C_6, preferably C_1-C_4, alkylsulphonyl (e.g. methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl), $-C(O)NR^{11}R^{12}$, $-NR^{13}C(O)-(NH)_pR^{14}$, phenyl, or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl).

Most preferably, each R^1 independently represents halogen (particularly chlorine or fluorine), cyano, nitro, C_1-C_6 alkoxy (especially methoxy), C_1-C_6 alkylcarbonyl (especially methylcarbonyl) or C_1-C_6 alkylcarbonylamino (particularly methylcarbonylamino). Each R^1 especially represents halogen or cyano.

Preferably X represents an oxygen atom or a CH_2 or NH group.

Preferred combinations of Y, Z^1 and Z^2 include:

Y	Z^1	Z^2
CH	CH_2	bond
CH	bond	CH_2
CH	CH_2	CH_2
CH	$(CH_2)_2$	bond
N	CH_2	CH_2

Q preferably represents an oxygen atom.

Each R^3 independently represents a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), $-CH_2OH$ or carboxyl group. It is preferred that R^3 represents a methyl, methoxycarbonyl, ethoxycarbonyl, $-CH_2OH$ or carboxyl group.

R^4, R^5, R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^4, R^5, R^6 and R^7 together represent a C_1-C_4 alkylene chain linking the two carbon atoms to which they are attached to form a 4- to 7-membered saturated carbocycle (e.g. cyclohexyl or preferably cyclopentyl), or R^5, R^6 and R^7 each represent a hydrogen atom and R^4 and R^8 together with the carbon atoms to which they are attached form a 5- to 6-membered saturated carbocycle (preferably cyclopentyl).

R^8 represents a hydrogen atom, a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or is linked to R^4 as defined above.

R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle.

R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by a C_1-C_6, preferably C_1-C_4, alkoxycarbonyl substituent group.

R^{13} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

R^{14} represents a hydrogen atom, or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl.

R^{15} represents a group C_2-C_6, preferably C_2-C_4, alkyl group (e.g. ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl or n-pentyl), C_2-C_6, preferably C_2-C_4, alkenyl, C_3-C_6 cycloalkyl (e.g. cyclobutyl or cyclopentyl), C_5-C_6 cycloalkenyl, adamantyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, wherein each group may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{17}.

The saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic) and may comprise up to four heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

Each R^{16} independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl

or cyclohexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), C_1-C_6, preferably C_1-C_4, haloalkoxy (e.g. trifluoromethoxy), $-NR^{18}R^{19}$, C_3-C_6 cycloalkylamino (e.g. cyclopropylamino, cyclobutylamino, cyclopentylamino or cyclohexylamino), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonylamino (e.g. methylcarbonylamino or ethylcarbonylamino), sulphonamido, C_1-C_6, preferably C_1-C_4, alkylsulphonyl (e.g. methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl), $-C(O)NR^{21}R^{22}$, $-NR^{23}C(O)-(NH)_vR^{24}$, phenyl, or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl).

Preferably, each R^{16} independently represents halogen (particularly chlorine or fluorine), cyano, C_1-C_4 alkoxy (especially methoxy), C_1-C_4 alkoxycarbonyl (especially methoxycarbonyl), C_1-C_4 haloalkyl (especially trifluoromethyl), C_1-C_4 alkylcarbonyl (particularly methylcarbonyl), phenyl or C_1-C_4 alkyl (e.g. methyl or tert-butyl). Each R^{16} is especially a halogen atom or methyl group.

R^{17} represents a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), amino or phenyl group.

R^{18} and R^{19} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^{19} and R^{20} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle.

R^{20} and R^{21} each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by a C_1-C_6, preferably C_1-C_4, alkoxycarbonyl substituent group.

R^{22} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

R^{23} represents a hydrogen atom, or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by carboxyl, C_1-C_6, preferably C_1-C_4, alkoxy or C_1-C_6, preferably C_1-C_4, alkoxycarbonyl.

Preferred compounds of the invention include:

N-(5-Chloro-2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isobutyramide,

Thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-[(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenylcarbamoyl)-methyl]-benzamide,

Pyrazine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclohexanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-phthalamic acid methyl ester,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-ureido-acetamide,

4-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-butyramide,

1-Acetyl-piperidine-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methoxy-benzamide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide,

Adamantane-1-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-phenyl-propionamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methoxy-benzamide,

5-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

1-Acetyl-pyrrolidine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

1,5-Dimethyl-1H-pyrazole-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

5-Oxo-pyrrolidine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

1H-Indole-6-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide,

Pentanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Pent-4-enoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclopentanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclopropanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isobutyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methylsulfanyl-acetamide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-butyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methoxy-acetamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2,2-dimethyl-propionamide,

5-Oxo-hexanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Hexanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

2-Chloro-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide,

3-Chloro-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide,

(4*R*)-*N*-(2-{3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-hydroxypropoxy}phenyl)-1,3-thiazolidine-4-carboxamide ditrifluoroacetate,

Thiophene-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-nicotinamide,

Pyridine-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isonicotinamide,

Cyclohexanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide,

5-Methyl-thiophene-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide,

Pentanoic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Pent-4-enoic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclopentanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide,

N-(2-{3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-hydroxypropoxy}phenyl)-2,2,2-trifluoroacetamide hydrochloride,

4-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenylcarbamoyl)-3-methyl-butyric acid,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-succinamic acid,

Furan-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

1H-Pyrrole-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclopentanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Methyl-isoxazole-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

[1,2,3]Thiadiazole-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-furan-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclopent-1-enecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

2-Methyl-furan-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Nitro-1H-pyrazole-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Furan-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

1H-Pyrrole-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Methyl-isoxazole-4-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-furan-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclopent-1-enecarboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

2-Methyl-furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

2,5-Dimethyl-furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-1H-pyrrole-2-carboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-3-thiophenecarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxy-2-methylpropyl)oxy]phenyl}-2-thiophenecarboxamide, compound with trifluoroacetic acid,

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-2-thiophenecarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]phenyl}-2-furancarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]phenyl}-1-pyrrole-2-carboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-1H-pyrrole-3-carboxamide,

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-2-furancarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxy-2-methylpropyl)oxy]phenyl}cyclopentanecarboxamide, compound with trifluoracetic acid,

N-(2-{3-[3-(4-Fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide,

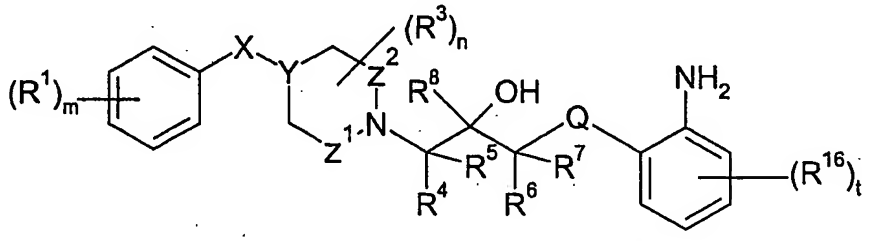
N-(2-{3-[3-(4-Cyano-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide, and

N-(2-{3-[4-(3,4-Dichloro-phenylamino)-piperidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises reacting a compound of general formula



(II)

or a salt thereof (e.g. an acid addition salt such as a hydrochloride salt), wherein m, n, t, R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^{16}, Q, Z^1 and Z^2 are as defined in formula (I), with a compound of general formula

$$R^{15} - CO_2H \qquad \text{(III)}$$

or chemically equivalent derivative thereof (e.g. acyl halide or anhydride derivative) wherein R^{15} is as defined in formula (I);

and optionally thereafter forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

The process of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as an alcohol (e.g. methanol or ethanol), a hydrocarbon (e.g. toluene), an amine (e.g. triethylamine or diisopropylethylamine) or acetonitrile at a temperature of, for example, 15°C or above, such as a temperature in the range from 20 to 120°C.

Compounds of formulae (II) and (III) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Examples of these conditions are:

(1) **(the respiratory tract)** airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

(8) diseases in which angiogenesis is associated with raised chemokine levels (e.g. NSCLC); and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention still further provides a method of treating an airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a

therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I) may be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form

of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The invention will now be further explained by reference to the following illustrative examples, in which ^{1}H NMR spectra were recorded on Varian Unity Inova 400. The central solvent peak of chloroform–*d* (δ_H 7.27 ppm) were used as internal standard. Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-Packard 1100 LC-MS system equipped with APCI /ESI ionisation chambers.
All solvents and commercial reagents were laboratory grade and used as received.
The nomenclature used for the compounds was generated with ACD/IUPAC Name Pro.
The following abbreviations are used in the examples:

NMP : 1-Methyl-2-pyrrolidinone
DIEA: N,N-Diisopropylethylamine
HBTU: 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HoBT: 1-Hydroxybenzotriazole
THF : Tetrahydrofuran

Example 1

***N*-(5-Chloro-2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isobutyramide**

a) *N*-(5-Chloro-2-hydroxy-phenyl)-isobutyramide

In a flask was added 4-chloro-2-aminophenol (1.2 g, 8.39 mmole) and water (25 ml). The suspension was vigorously stirred and isobutyric anhydride (1.6 ml, 10.5 mmole) was added. The mixture was heated to 60°C for 30 minutes under vigorous stirring. The emulsion was cooled, and a precipitate was formed, which was collected through filtration. The solid was washed twice with water on the filter and was finally dried to give 1.4 g (78%) of the sub-title compound as a white solid.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ: 10.11 (1H, s); 9.12 (1H, s); 7.94 (1H, d, *J* 2.5 Hz); 6.95 (1H, dd, *J* 8.7 2.6 Hz); 6.84 (1H, d, *J* 8.5 Hz); 2.79 (1H, p, *J* 6.7 Hz); 1.08 (6H, d, *J* 6.8 Hz)

b) *N*-(5-Chloro-2-oxiranylmethoxy-phenyl)-isobutyramide

In a vial was added the compound obtained in a) (0.4 g, 1.87 mmole), epibromohydrin (0.28 g, 2.06 mmole), K_2CO_3 (0.5 g, 3.7 mmole) and DMF (2 ml). The vial was sealed and heated with stirring (2 hours, 60°C). The mixture was then partitioned between EtOAc and water, and the organic phase was washed twice with water and once with brine, and was finally evaporated to give a brown solid. The crude epoxide was purified on silica, to give 0.22 g (44%) of the sub-title compound as a white solid.

c) In a vial was added the compound obtained in b) (0.026 g, 0.13 mmole), 3-(4-chlorophenoxy)-pyrrolidine (0.035 g, 0.13 mmole) in ethanol (2 ml). The vial was sealed and heated with stirring at 75°C for 3 hours. The solution was allowed to cool, and the solvent was evaporated. The crude product was purified on silica, and the pure fractions were collected. The title compound was lyophilized as the hydrochloride, giving 0.055 g (84%) as a white solid. The compound was a mixture of four stereoisomers, which had an effect on the NMR-spectra.

^{1}H-NMR (400 MHz, DMSO-*d6*) δ: 10.84-10.34 (1H, m); 9.12 (1H, s); 8.09 (1H, s); 7.36 (2H, dd, *J* 9.2 1.3 Hz); 7.11-7.00 (3H, m); 7.00 (2H, d, *J* 8.8 Hz); 6.22-6.06 (1H, m); 5.22-5.10 (1H, m); 4.34 (1H, bs); 4.08-3.96 (1.5H, m); 3.95-3.87 (1H, m); 3.83-3.66 (1.5H, m); 3.61-3.23 (3H, m); 2.86 (1H, sept, *J* 6.6 Hz); 2.64-2.51 ($^1/_2$H, m); 2.36-2.14 (1H, m); 2.14-2.00 ($^1/_2$H, m); 1.08 (6H, d, *J* 6.7 Hz)

APCI-MS: m/z 467.2 [MH+]

Aniline Intermediate 1

1-(2-aminophenoxy)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-propanol dihydrochloride

N-(2-{3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-hydroxypropoxy}phenyl)acetamide (1.418g, 3.13 mmol, prepared by analogy to Example 1) was dissolved in 50ml HCl (35%/aq, puriss) and refluxed overnight. The product precipitated and was filtered and dried to give 0.835 g (65%) of the title compound.

APCI-MS m/z: 411, 413 [MH^+]

^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.39-3.31 (m, 2H), 7.31(d, 1H), 7.01-6.98(m, 3H), 6.94-6.91(m, 1H), 6.75(dd, 1H), 4.31(m, 1H), 4.12-4.02 (m, 2H), 3.92(dd, 1H), 2.90(m, 1H), 2.69(m, 1H), 2.62-2.51(m, 2H), 2.46(dd, 1H), 2.34(m, 1H), 2.18(s, 3H), 2.04-1.93(m, 2H), 1.89-1.77(m, 2H).

Aniline Intermediate 2

1-[(2-aminophenyl)oxy]-3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-propanol dihydrochloride

Prepared according to the method described in Aniline Intermediate 1.

APCI-MS m/z: 363, 365 [MH^+]

The intermediate anilines 1 and 2 described above were used in the following examples.

Example 2

Thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

To a solution of 80 uL 0.2M 2-thiophenecarboxylic acid in NMP were HBTU (80uL, 0.2M/NMP) ,HoBT (80uL, 0.2M/NMP), DIEA (30uL, 0.5M/NMP) and pyridine (30uL, 0.5M/NMP) added and stirred for 30 minutes before 1-[(2-aminophenyl)oxy]-3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-propanol (75uL, 0.2M/NMP) was added. The mixture was stirred overnight at roomtemperature before it was concentrated under reduced

pressure to dryness. The product was diluted with 1000uL dichloromethane and washed with with sat.$NaHCO_3$/aq (800uL), 1.8%HCl/aq(800uL) and sat. NaCl/aq.
The organic layer was concentrated under reduced pressure to dryness and used without further purification. Yield 3.6mg, 51%

APCI-MS m/z: 473.2 [MH^+]
^1H NMR (400 MHz, CD_3OD) : δ 7.88-7.85 (d, 1H), 7.74-7.65 (m, 2H), 7.34-7.28 (m, 2H), 7.27-7.21(m, 1H), 7.20-7.15 (m, 1H), 7.14-7.09 (dd, 1H), 7.06-7.00 (m, 1H), 6.96-6.91 (m, 2H), 5.18-5.12 (m, 1H), 4.39-4.30 (m, 1H), 4.19-3.24 (m, 9H), 2.66-2.11 (m, 3H)

The following Examples 3 to 53 were prepared by methods analogous to the method described in Example 2.

Example 3

N-[(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenylcarbamoyl)-methyl]-benzamide

APCI-MS m/z: 524.3 [MH^+]

Example 4

Pyrazine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 469.2 [MH^+]

Example 5

Cyclohexanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 473.3 [MH^+]

Example 6

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-phthalamic acid methyl ester

APCI-MS m/z: 525.2 [MH^+]

Example 7

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide

APCI-MS m/z: 449.2 [MH^+]

Example 8

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-ureido-acetamide

APCI-MS m/z: 463.2 [MH^+]

Example 9

4-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-butyramide

APCI-MS m/z: 490.3 [MH^+]

Example 10

1-Acetyl-piperidine-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 516.3 [MH^+]

Example 11

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methoxy-benzamide

APCI-MS m/z: 497.2 [MH^+]

Example 12

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide

APCI-MS m/z: 504.3 [MH^+]

Example 13

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide

APCI-MS m/z: 506.2 [MH^+]

Example 14

Adamantane-1-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 525.3 [MH^+]

Example 15

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-phenyl-propionamide

APCI-MS m/z: 552.3 [MH^+]

Example 16

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methoxy-benzamide

APCI-MS m/z: 497.2 [MH^+]

Example 17

5-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 487.2 [MH^+]

Example 18

1-Acetyl-pyrrolidine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 502.3 [MH^+]

Example 19

1,5-Dimethyl-1H-pyrazole-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 485.3 [MH^+]

Example 20

5-Oxo-pyrrolidine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 474.2 [MH^+]

Example 21

1H-Indole-6-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 506.2 [MH^+]

Example 22

Cyclobutanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 445.3 [MH^+]

Example 23

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide

APCI-MS m/z: 419.2 [MH^+]

Example 24

Pentanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 447.3 [MH^+]

Example 25

Pent-4-enoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 445.3 [MH^+]

Example 26

Cyclopentanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 459.3 [MH^+]

Example 27

Cyclopropanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 431.2 [MH^+]

Example 28

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isobutyramide

APCI-MS m/z: 433.3 [MH^+]

Example 29

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methylsulfanyl-acetamide

APCI-MS m/z: 451.2 [MH^+]

Example 30

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide

APCI-MS m/z: 476.2 [MH^+]

Example 31

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-butyramide

APCI-MS m/z: 433.3 [MH^+]

Example 32

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide

APCI-MS m/z: 447.3 [MH^+]

Example 33

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methoxy-acetamide

APCI-MS m/z: 435.2 [MH^+]

Example 34

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2,2-dimethyl-propionamide

APCI-MS m/z: 447.2 [MH^+]

Example 35

5-Oxo-hexanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 475.3 [MH^+]

Example 36

Hexanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 461.3 [MH^+]

Example 37

2-Chloro-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide

APCI-MS m/z: 501.2 , 503.2 [MH^+]

Example 38

3-Chloro-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide

APCI-MS m/z: 501.2 , 503.2 [MH^+]

Example 39

(4*R*)-*N*-(2-{3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-hydroxypropoxy}phenyl)-1,3-thiazolidine-4-carboxamide ditrifluoroacetate

APCI-MS m/z: 478.2 [MH^+]

Example 40

Thiophene-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 521.0 , 523.0 [MH^+]

Example 41

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide

APCI-MS m/z: 515.2 , 517.2[MH^+]

Example 42

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-nicotinamide

APCI-MS m/z: 516.2 , 518.2 [MH^+]

Example 43

Pyridine-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 516.2 , 518.2 [MH^+]

Example 44

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isonicotinamide

APCI-MS m/z: 516.2 , 518.2 [MH^+]

Example 45

Cyclohexanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 521.3 , 523.3 [MH^+]

Example 46

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide

APCI-MS m/z: 497.2 , 499.3 [MH^+]

Example 47

5-Methyl-thiophene-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 535.2 , 537.2 [MH^+]

Example 48

Cyclobutanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z:493.3 , 495.2 [MH^+]

Example 49

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide

APCI-MS m/z: 467.2 , 469.2 [MH^+]

Example 50

Pentanoic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 495.3 , 497.3 [MH^+]

Example 51

Pent-4-enoic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 493.3 ,495.2 [MH^+]

Example 52

Cyclopentanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide

APCI-MS m/z: 507.3 , 509.3 [MH^+]

Example 53

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide

APCI-MS m/z: 495.3, 497.3 [MH^+]

Example 54

***N*-(2-{3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-hydroxypropoxy}phenyl)-2,2,2-trifluoroacetamide hydrochloride**

A mixture of 1-(2-aminophenoxy)-3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-propanol (10mg, 0.022mmol), dichloromethane (3ml) and Triethyl amine was cooled in an ice bath. A solution of Trifluoro acetic anhydride (3.5µl, 0.025mmol) in dichloromethane (2ml) was then added and the mixture stirred at 0°C until reaction completion. The mixture was diluted with dichloromethane, washed with 1M H_2SO_4, water, dried over natrium sulphate and concentrated to give an oil. The oil was treated with 1.0M ethereal HCl solution to give the product as solid (9mg).

APCI-MS: m/z 459, 460 [MH^+]

Example 55

4-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenylcarbamoyl)-3-methyl-butyric acid

1-(2-aminophenoxy)-3-[4-(3,4-dichlorophenoxy)-1-piperidinyl]-2-propanol (75uL, 0.2M/NMP) was mixed with 3-methyl glutaric anhydride (3eq, 225uL 0.2M /NMP) to get a product containing both esther and amide. After evaporation of the mixture it was treated with 3 eq 0.5M LiOH in (THF/water 1:4) for two hours at 80°C to hydrolyse the esther. The reaction mixture was diluted with more water (2mL) and the desired product was extracted with 5x500uL EtOAc which was evaporated to dryness.

APCI-MS m/z: 539.2 , 541.2 [MH^+]

Example 56

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-succinamic acid

Prepared according to the method described in Example 55.

APCI-MS m/z: 511.2 , 513.2 [MH^+]

Aniline Intermediate 3

1-(2-amino-5-methylphenoxy)-3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-propanol

APCI-MS m/z: 377.2 , 379.1 [MH+]

^{1}H NMR (400 MHz, CDCl3) : δ 7.26-7.21 (m, 2H), 6.79-6.74 (m, 2H), 6.67-6.62 (m, 3H), 4.83-4.76 (m, 1H), 4.15-4.06 (m, 1H), 4.04-4.00 (d, 2H), 3.73-3.64 (s, 2H), 3.47-3.35 (s, 1H), 3.14 –2.56 (m, 6H), 2.36-2.22(m, 4H), 2.05-1.95(m, 1H)

Aniline Intermediate 4

1-(2-amino-5-methylphenoxy)-3-[3-(4-fluorophenoxy)-1-pyrrolidinyl]-2-propanol

APCI-MS m/z: 361.1 [MH+]

^{1}H NMR (400 MHz, CDCl3) : δ 7.00-6.94 (m, 2H), 6.81-6.76 (m, 2H), 6.67-6.62 (m, 3H), 4.81-4.74 (m, 1H), 4.15-4.06 (m, 1H), 4.03-3.99 (m, 2H), 3.88-3.36 (m, 3H), 3.12 –2.56 (m, 6H), 2.33-2.23(m, 4H), 2.05-1.96(m, 1H)

The compounds of Examples 57 to 85 were prepared using one of the Aniline Intermediates 3 and 4.

Example 57

Furan-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 471.5 , 473.5 [MH+]

Example 58

1H-Pyrrole-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 470.5 , 472.5 [MH+]

Example 59

Thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 487.5 , 489.5 [MH+]

Example 60

Cyclopentanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 473.6 , 475.5 [MH+]

Example 61

5-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 501.5 , 503.5 [MH+]

Example 62

3-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 521.5 , 532.5 [MH+]

Example 63

5-Methyl-isoxazole-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 486.5 , 488.6 [MH+]

Example 64

[1,2,3]Thiadiazole-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 489.5 , 491.5[MH+]

Example 65

3-Methyl-furan-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 485.5 , 487.6 [MH+]

Example 66

Cyclopent-1-enecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 471.6 , 473.6 [MH+]

Example 67

2-Methyl-furan-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 485.6 , 487.6 [MH+]

Example 68

3-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 501.6 , 503.5 [MH+]

Example 69

5-Nitro-1H-pyrazole-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 516.5 , 518.5 [MH+]

Example 70

Thiophene-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 487.5 , 489.5 [MH+]

Example 71

Cyclobutanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 459.5 , 461.5 [MH+]

Example 72

Furan-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 455.5 [MH+]

Example 73

1H-Pyrrole-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 454.6 [MH+]

Example 74

Thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 471.5 [MH+]

Example 75

3-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 505.5 , 507.5 [MH+]

Example 76

5-Methyl-isoxazole-4-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 470.5 [MH+]

Example 77

3-Methyl-furan-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 469.6 [MH+]

Example 78

Cyclopent-1-enecarboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 455.6 [MH+]

Example 79

2-Methyl-furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrr lidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 469.6 [MH+]

Example 80

3-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 485.5 [MH+]

Example 81

5-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 505.5 , 507.5 [MH+]

Example 82

Thiophene-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 471.5 [MH+]

Example 83

2,5-Dimethyl-furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 483.6 [MH+]

Example 84

Cyclobutanecarboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 443.6 [MH+]

Example 85

Furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide

APCI-MS m/z: 455.5 [MH+]

Example 86

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-1H-pyrrole-2-carboxamide

APCI-MS: m/z 454.1 [$M+H^+$]

Example 87

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-3-thiophenecarboxamide

APCI-MS: m/z 471.1 [$M+H^+$]

Example 88

***N*-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxy-2-methylpropyl)oxy]phenyl}-2-thiophenecarboxamide, compound with trifluoroacetic acid**

Aniline intermediate 3 (60 mg, 0.159 mmol), 2-thiophenecarboxylic acid (20.4 mg, 0.159 mmol) and HATU (72 mg, 0.191 mmol) were stirred in dichloromethane (2 ml).

Diisopropylethylamine was added to pH 8. The mixture was stirred overnight and then concentrated. The residue was purified on silica (dichloromethane/methanol 98/2) followed by purification on C18 (2 g Isolute, acetonitrile/water 20/80 to 35/65 with 0.5% trifluoroacetic acid) to give the title compound (75 mg, 79%).

^{1}H-NMR (400 MHz, MeOD): δ 7.86 (m, 1H), 7.72 (m, 1H), 7.50 (m, 1H), 7.29 (m, 3H), 7.16 (m, 2H), 7.07 (m, 1H), 6.91 (m, 2H), 5.10 (m, 1H), 3.82-4.17 (m, 4H), 3.24-3.69 (m, 4H), 2.13-2.64 (m, 2H), 1.38 (m, 3H).

MS-APCI+: m/z 487 [MH^+]

Example 89

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-2-thiophenecarboxamide

APCI MS APCI-MS: m/z 471.1 [$M+H^+$]

Example 90

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]phenyl}-2-furancarboxamide

APCI-MS: m/z 456.9 [$M+H^+$]

Example 91

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]phenyl}-1-pyrrole-2-carboxamide

APCI-MS: m/z 456.1 [$M+H^+$]

Example 92

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-1H-pyrrole-3-carboxamide

APCI-MS: m/z 470.0 [M+H$^+$]

Example 93

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-2-furancarboxamide

APCI-MS: m/z 455.1 [M+H$^+$]

Example 94

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxy-2-methylpropyl)oxy]phenyl}cyclopentanecarboxamide, compound with trifluoracetic acid

The compound (80 mg, 86%) was prepared from aniline intermediate 3 (60 mg, 0.159 mmol) and cyclopentanecarboxylic acid (18 µl, 0.159 mmol) as described in Example 88.

^{1}H-NMR (400 MHz, MeOD): δ 7.59 (m, 1H), 7.29 (m, 2H), 7.19 (m, 1H), 7.09 (m, 1H), 6.97 (m, 3H), 5.17 (m, 1H), 3.86-4.23 (m, 4H), 3.35-3.73 (m, 4H), 2.86 (m, 1H), 1.45 (bs, 3H).

MS-APCI+: m/z 473 [MH$^+$]

Example 95

N-(2-{3-[3-(4-Fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide

The compound was prepared using an analogous method as in Example 88.

APCI-MS: m/z 465 [MH^+]

Example 96

N-(2-{3-[3-(4-Cyano-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide

The compound was prepared using an analogous method as in Example 88.

APCI-MS: m/z 472 [MH^+]

Example 97

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide

The compound was prepared using an analogous method as in Example 88.

APCI-MS: m/z 529 [MH^+]

Example 98

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide

The compound was prepared using an analogous method as in Example 88.

APCI-MS: m/z 481 [MH^+]

Example 99

N-(2-{3-[4-(3,4-Dichloro-phenylamino)-piperidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide

The compound was prepared using an analogous method as in Example 88.

APCI-MS: m/z 528 [MH^+]

5

THP-1 Chemotaxis Assay

Introduction

The assay measured the chemotactic response elicited by MIP-1α chemokine in the human monocytic cell line THP-1. The compounds of the Examples were evaluated by their
10 ability to depress the chemotactic response to a standard concentration of MIP-1α chemokine.

Methods

Culture of THP-1 cells

15 Cells were thawed rapidly at 37°C from frozen aliquots and resuspended in a 25 cm flask containing 5 ml of RPMI-1640 medium supplemented with Glutamax and 10% heat inactivated fetal calf serum without antibiotics (RPMI+10%HIFCS). At day 3 the medium is discarded and replaced with fresh medium.

20 THP-1 cells are routinely cultured in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum and glutamax but without antibiotics. Optimal growth of the cells requires that they are passaged every 3 days and that the minimum subculture density is 4x10+5 cells/ml.

25 **Chemotaxis assay**

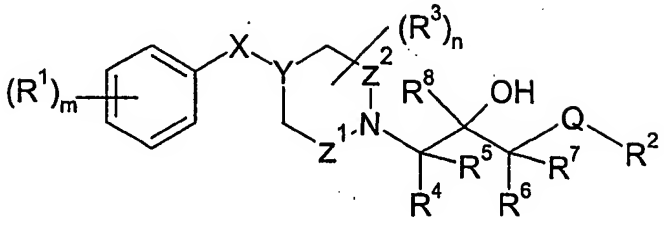
Cells were removed from the flask and washed by centrifugation in RPMI+10%HIFCS+glutamax. The cells were then resuspended at 2x10+7 cells/ml in fresh medium (RPMI+10%HIFCS+glutamax) to which was added calcein-AM (5 µl of stock solution to 1 ml to give a final concentration of $5x10^{-6}$M). After gentle mixing the
30 cells were incubated at 37°C in a CO_2 incubator for 30 minutes. The cells were then

diluted to 50 ml with medium and washed twice by centrifugation at 400xg. Labelled cells were then resuspended at a cell concentration of 1x10+7 cells/ml and incubated with an equal volume of MIP-1α antagonist (10^{-10}M to 10^{-6}M final concentration) for 30 minutes at 37°C in a humidified CO_2 incubator.

Chemotaxis was performed using Neuroprobe 96-well chemotaxis plates employing 8 μm filters (cat no. 101-8). Thirty microlitres of chemoattractant supplemented with various concentrations of antagonists or vehicle were added to the lower wells of the plate in triplicate. The filter was then carefully positioned on top and then 25μl of cells preincubated with the corresponding concentration of antagonist or vehicle were added to the surface of the filter. The plate was then incubated for 2 hours at 37°C in a humidified CO_2 incubator. The cells remaining on the surface were then removed by adsorption and the whole plate was centrifuged at 2000 rpm for 10 minutes. The filter was then removed and the cells that had migrated to the lower wells were quantified by the fluorescence of cell associated calcein-AM. Cell migration was then expressed in fluorescence units after subtraction of the reagent blank and values were standardized to % migration by comparing the fluorescence values with that of a known number of labelled cells. The effect of antagonists was calculated as % inhibition when the number of migrated cells were compared with vehicle.

CLAIMS

1. A compound of general formula



(I)

wherein:

m is 0, 1, 2 or 3;

each R^1 independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^9R^{10}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido, C_1-C_6 alkylsulphonyl, $-C(O)NR^{11}R^{12}$, $-NR^{13}C(O)-(NH)_pR^{14}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

p is 0 or 1;

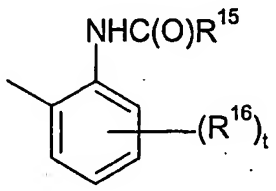
X represents an oxygen atom or a CH_2, OCH_2, CH_2O, CH_2NH, NH, carbonyl or sulphonyl group and Y represents a nitrogen atom or a CH or C(OH) group, provided that when X represents an oxygen atom or a CH_2O, CH_2NH or NH group, then Y represents a CH group;

Z^1 represents a bond or a group $(CH_2)_q$ where q is 1 or 2;

Z^2 represents a bond or a group CH_2, with the proviso that Z^1 and Z^2 do not both simultaneously represent a bond;

Q represents an oxygen or sulphur atom or a group CH_2 or NH;

R^2 represents a group



;

n is 0, 1 or 2;

each R^3 independently represents a C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl, -CH_2OH or carboxyl group;

R^4, R^5, R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^4, R^5, R^6 and R^7 together represent a C_1-C_4 alkylene chain linking the two carbon atoms to which they are attached to form a 4- to 7-membered saturated carbocycle, or R^5, R^6 and R^7 each represent a hydrogen atom and R^4 and R^8 together with the carbon atoms to which they are attached form a 5- to 6-membered saturated carbocycle;

R^8 represents a hydrogen atom, a C_1-C_6 alkyl group or is linked to R^4 as defined above;

R^9 and R^{10} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

R^{13} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{14} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl;

R^{15} represents a group C_2-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, adamantyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, wherein each group may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{17}, with the proviso that R^{15} does not represent an unsubstituted 1-pyrrolidinyl, an unsubstituted 1-piperidinyl or an unsubstituted 1-hexamethyleneiminyl group;

t is 0, 1, 2 or 3;

each R^{16} independently represents halogen, cyano, nitro, carboxyl, hydroxyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NR^{18}R^{19}$, C_3-C_6 cycloalkylamino, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, sulphonamido ($-SO_2NH_2$), C_1-C_6 alkylsulphonyl, $-C(O)NR^{20}R^{21}$, $-NR^{22}C(O)(NH)_vR^{23}$, phenyl, or C_1-C_6 alkyl optionally substituted by carboxyl or C_1-C_6 alkoxycarbonyl;

R^{17} represents a C_1-C_6 alkyl, amino or phenyl group;

R^{18} and R^{19} each independently represent a hydrogen atom or a C_1-C_6 alkyl group, or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle;

R^{20} and R^{21} each independently represent a hydrogen atom or a C_1-C_6 alkyl group optionally substituted by C_1-C_6 alkoxycarbonyl;

v is 0 or 1;

R^{22} represents a hydrogen atom or a C_1-C_6 alkyl group; and

R^{23} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by carboxyl, C_1-C_6 alkoxy or C_1-C_6 alkoxycarbonyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein X represents an oxygen atom or a CH_2 or NH group.

3. A compound according to claim 1, wherein Y represents a CH group.

4. A compound according to any one of claims 1 to 3, wherein Q represents an oxygen atom.

5. A compound according to any one of claims 1 to 4, wherein R^{15} represents a group C_2-C_5 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, adamantyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, wherein each group may

be optionally substituted by one, two or three substituents independently selected from hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{17}.

6. A compound according to claim 5, wherein the saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one heteroatom selected from nitrogen, oxygen and sulphur, is pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, thiadiazolyl, isoxazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl or pyridinyl.

7. A compound according to any one of claims 1 to 6, wherein each R^{16} independently represents halogen, cyano, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_4 haloalkyl, C_1-C_4 alkylcarbonyl, phenyl or C_1-C_4 alkyl.

8. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 1 being selected from:

N-(5-Chloro-2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isobutyramide,

Thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-[(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenylcarbamoyl)-methyl]-benzamide,

Pyrazine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclohexanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-phthalamic acid methyl ester,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-ureido-acetamide,

4-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-butyramide,

1-Acetyl-piperidine-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methoxy-benzamide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide,

Adamantane-1-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-phenyl-propionamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methoxy-benzamide,

5-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

1-Acetyl-pyrrolidine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

1,5-Dimethyl-1H-pyrazole-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

5-Oxo-pyrrolidine-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

1H-Indole-6-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide,

Pentanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Pent-4-enoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclopentanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclopropanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isobutyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methylsulfanyl-acetamide,

2-Acetylamino-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-butyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2-methoxy-acetamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-2,2-dimethyl-propionamide,

5-Oxo-hexanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Hexanoic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

2-Chloro-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide,

3-Chloro-N-(2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide,

(4*R*)-*N*-(2-{3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-hydroxypropoxy}phenyl)-1,3-thiazolidine-4-carboxamide ditrifluoroacetate,

Thiophene-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-benzamide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-nicotinamide,

Pyridine-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-isonicotinamide,

Cyclohexanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-hydroxy-butyramide,

5-Methyl-thiophene-2-carboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-propionamide,

Pentanoic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Pent-4-enoic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

Cyclopentanecarboxylic acid (2-{3-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-amide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-3-methyl-butyramide,

N-(2-{3-[3-(4-chlorophenoxy)-1-pyrrolidinyl]-2-hydroxypropoxy}phenyl)-2,2,2-trifluoroacetamide hydrochloride,

4-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenylcarbamoyl)-3-methyl-butyric acid,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-propoxy}-phenyl)-succinamic acid,

Furan-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

1H-Pyrrole-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclopentanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Methyl-isoxazole-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

[1,2,3]Thiadiazole-4-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-furan-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclopent-1-enecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

2-Methyl-furan-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Nitro-1H-pyrazole-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-3-carboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[3-(4-chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Furan-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

1H-Pyrrole-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Methyl-isoxazole-4-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-furan-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclopent-1-enecarboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

2-Methyl-furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

3-Methyl-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

5-Chloro-thiophene-2-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Thiophene-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

2,5-Dimethyl-furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Cyclobutanecarboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

Furan-3-carboxylic acid (2-{3-[3-(4-fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-propoxy}-4-methyl-phenyl)-amide,

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-1H-pyrrole-2-carboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-3-thiophenecarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxy-2-methylpropyl)oxy]phenyl}-2-thiophenecarboxamide, compound with trifluoroacetic acid,

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-2-thiophenecarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]phenyl}-2-furancarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]phenyl}-1-pyrrole-2-carboxamide

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-1H-pyrrole-3-carboxamide,

N-{2-[(3-{3-[(4-fluorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxypropyl)oxy]-4-methylphenyl}-2-furancarboxamide,

N-{2-[(3-{3-[(4-chlorophenyl)oxy]-1-pyrrolidinyl}-2-hydroxy-2-methylpropyl)oxy]phenyl}cyclopentanecarboxamide, compound with trifluoracetic acid,

N-(2-{3-[3-(4-Fluoro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide,

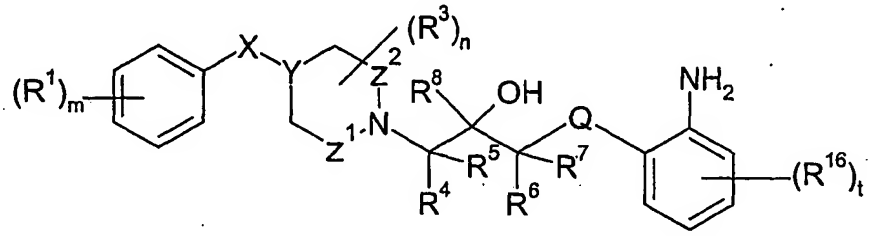
N-(2-{3-[3-(4-Cyano-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide,

N-(2-{3-[4-(3,4-Dichloro-phenoxy)-piperidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide,

N-(2-{3-[3-(4-Chloro-phenoxy)-pyrrolidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide, and

N-(2-{3-[4-(3,4-Dichloro-phenylamino)-piperidin-1-yl]-2-hydroxy-2-methyl-propoxy}-phenyl)-benzamide.

9. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises reacting a compound of general formula



(II)

or a salt thereof, wherein m, n, t, R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^{16}, Q, Z^1 and Z^2 are as defined in formula (I), with a compound of general formula

$$R^{15} - CO_2H \qquad \text{(III)}$$

or chemically equivalent derivative thereof, wherein R^{15} is as defined in formula (I); and optionally thereafter forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained.

10. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A process for the preparation of a pharmaceutical composition as claimed in claim 10 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 for use in therapy.

13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in therapy.

14. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

15. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating rheumatoid arthritis.

16. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.

17. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating asthma.

18. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating multiple sclerosis.

19. A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8.

20. A method of treating an airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01378

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/46, C07D 211/58, C07D 211/22, C07D 207/12, C07D 295/08, C07D 295/10, A61K 31/295

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0035449 A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June 2000 (22.06.00) --	1-18
A	WO 0035451 A1 (DU PONT PHARMACEUTICALS COMPANY), 22 June 2000 (22.06.00) --	1-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2001	14 -11- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01378

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 01/01378

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0035449 A1	22/06/00	AU 1940600 A	03/07/00
		AU 2057200 A	03/07/00
		AU 2482100 A	03/07/00
		AU 3126600 A	03/07/00
		AU 3126700 A	03/07/00
		AU 4820699 A	01/02/00
		BR 9911920 A	27/03/01
		EP 1099266 A	16/05/01
		NO 20010071 A	08/03/01
		NO 20012977 A	20/08/01
		US 6087034 A	11/07/00
		WO 0003445 A	20/01/00
		WO 0035451 A	22/06/00
		WO 0035452 A	22/06/00
		WO 0035453 A	22/06/00
		WO 0035454 A	22/06/00
		AU 3634001 A	08/05/01
		WO 0130752 A	03/05/01
WO 0035451 A1	22/06/00	AU 1940600 A	03/07/00
		AU 2057200 A	03/07/00
		AU 2482100 A	03/07/00
		AU 3126600 A	03/07/00
		AU 3126700 A	03/07/00
		AU 4820699 A	01/02/00
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		EP 1099266 A	16/05/01
		NO 20010071 A	08/03/01
		NO 20012977 A	20/08/01
		US 6087034 A	11/07/00
		WO 0003445 A	20/01/00
		WO 0035449 A	22/06/00
		WO 0035452 A	22/06/00
		WO 0035453 A	22/06/00
		WO 0035454 A	22/06/00